Computer exercises

Running IDL exercises:

- The IDL virtual machine has to be installed at your own computer (from USB memory stick)
- Please as “Administrator” at your own PC/Mac copy the files from the memory stick to your own computer (it makes installation a lot faster to copy installation files):
    - IDL Runtime environment installation file from idl_install_873:
        - For Windows (64 bit): idl873_win.exe
        - For MAC (64 bit): idl873_mac.pkg
        - Only copy the file that fits your operating system
    - Course exercise: idl_exercise (total directory and memorize where you put it)
    - When finished copying give memory stick to next participant
- As “Administrator” run the installation of IDL, either the .pkg file for mac or the .exe file for windows. When asked deselect the “Dicom Network Services” and “DataMiner”, and press cancel when asked to run the “Harris administrator now”. We only use IDL as an engine which doesn’t require a license and administration.
- When installed reboot your PC/Mac.
- The course exercises are then started by clicking at the “pkcourse.sav” file in the idl_exercise directory.
- **Mac OS**
    - For the Mac the X11 (XQuartz) and the Java SE software have to be installed. When you click the pkcourse.sav file it finds out automatically if present. It then should ask you to install the software, do that either from MAC software shop, or from the “Mac-XQuartz-Java” directory at the USB memory stick. Be sure that it is correct version for your operating system

MR exercise at NRU computers (Thursday afternoon):

- We are using computers at NRU (5th floor Nordfløj 2, NF2, 8057)
- Windows login (ctrl+alt+del, username: course0, password: KinCourse2024)
- We use Thinlinc to start a login at the unix system, please start that and select to connect to server “krogh.nru.dk”
- You then login to the unix system (username: course1-10, password: KinCourse2024)
- Then from a terminal “ssh -l course0 lehmann” with password: “KinCourse2024”.
- Start matlab by typing “matlab” in the Xterm
- Then follow instructions in MR course description

Checking email and internet access

- You should be able to connect to the SSID: “RegH Gaest” network. When connected you are asked to create an account using your email address, and a mobile phone number.

PC Exercise 1: Fitting one or two exponentials to a curve

Purpose

This exercise should teach you to look at a curve and guess how many exponential functions that should be used to describe it. Furthermore, the purpose is to get an idea of how to fit rate-constants to exponential curves.

Questions

idlcourse: Exercise 1a: Exponentials
You select a sample curve (6 different choices) and then have to decide if it is a one or two exponential function. You can then enter initial values and rate constants using either the scroll bar or by entering a number in the box (remember to finish this with a “enter”).

Fitting: one exponential

Here you have to fit the curve seen with a one exponential function $\mathbf{y = C_0 e^{-k \cdot t}}$. $\mathbf{C_0}$ is the initial amplitude while **k** is the rate constant. The plot at the lower left shows the residuals (measurement - model output). The lower the absolute value of the residuals, the better is the fit.

- How/where can you read the initial amplitude on the exponential curve?
- How do you find/calculate the rate constant when you have an exponential curve/function?
- What are the initial amplitude and the rate constant of the optimal fit?
- Try to change the initial value and the rate constant to see how the curve behaves differently. How do the initial amplitude and the rate constant influence the curve-fit?
- Find different ways of estimating the rate constant for the exponential curve?

Fitting: two exponentials

Here you have to fit the curve seen with a two exponential function $\mathbf{y = C_1 e^{-k_1 \cdot t} + C_2 e^{-k_2 \cdot t}}$.

<u>Answer these questions before running the program</u>.

- How do you separate the two exponentials when you have a double exponential curve?
- Guess the rate constant for the “fast” exponential?
- Guess the rate constant for the “slow” exponential?
- Guess the initial value for the “slow” exponential?
- Guess the initial value for the “fast” exponential?

When you input your guess of the parameters, C_i and k_i, the program will show the fitted function curve and the differences between the function and the measured data (residuals).

- Look at the function plot and the residuals plot, adjust your parameters to minimize the residuals.
- How does the change of the parameters influence the scale and shape of the function curve?

It is less obvious how and which parameters to change in order to improve the fit, when there are more variables. When the fitting is close, try to reveal one of the true values, and work on the remaining ones.

PC Exercise 2: Convolution and Extraction

idlcourse: Exercise 1b: Convolution

Purpose

This exercise should give you an idea of how convolution is performed, what it does and what it is used for. When you have an input to a system, and observe the output from the system, you should be able to understand what the system response function does to the input.

Convolution

To remind you, a convolution looks like this: $\mathbf{y(t)} = \int_{\tau=0}^{\mathbf{t}} \mathbf{I(\tau) \cdot R(t-\tau)d\tau = I(t) \otimes R(t)}$, where **I(t)** is the input function, **R(t)** is the impulse response function and **y(t)** is the output from the system.

Select an input, start out with one of the simple ones, Constant. Select a simple impulse response, e.g. Delta.

- Observe the measured output. How does it compare to the input function?

Keep the input function as Constant, select one-exponential function as the impulse response

- What would then happen to the observed system output, and why?
- How is the output generated from the impulse response at each time step?

Select a more sophisticated input, e.g. bolus+infusion

- What would then happen to the observed system output, and why?

- Can you generate the same output by having a sophisticated input and a simple impulse response, as by having a simple system input and a sophisticated impulse response?

idlcourse: Exercise 1c: Extraction

Purpose

This exercise shows the relationship between the rate constant K_1 and permeability/flow F, and between extraction E and permeability/flow F for a PS values, which yourself have to choose (upper graphs).

Extraction

HMPAO (SPECT flow tracer) has an extraction of 60% at normal flow 0.5 min^{-1}.

- Does K_1 have a linear response in the normal flow interval (0 – 0.5 min^{-1})?

H2O (PET flow tracer) has an extraction of 80% at normal flow 0.5 min^{-1}.

- Does K_1 have a linear response in the normal flow interval (0 – 0.5 min^{-1})?

FDG (PET glucose tracer) has an extraction of 10% at normal flow 0.5 min^{-1}.

- Does K_1 have a linear response in the normal flow interval (0 – 0.5 min^{-1})?
- How does this tracer react to an increase in the perfusion (flow)?

Why would it be preferred to have a high extraction rate when measuring flow changes?

In the lower graphs the relationship between the rate constant, K_1 and permeability surface area product, PS, and between extraction, E and permeability surface area product, PS for a fixed flow F can be tested. You can yourself vary the flow F and inspect how a different value of the PS product varies K1 and Extraction.

- If we want a tracer not vulnerable to flow changes, what will then be the limit for PS?

Hint: when x is very small, $\exp(-x) \approx 1 - x$

PC Exercise 3: 1-tissue model simulation, Models and rate constants

idlcourse: Exercise 2: Models and rate constants

Purpose

By exploring the elementary principles of PET kinetic modelling, you will get a feeling for the compartmental model configuration (single-tissue, two-tissue irreversible and two-tissue reversible compartment models), how the individual rate constants affect the shape and scale of the time activity curves (TACs), and how to evaluate the goodness-of-fit, etc.

Models and rate constants

Seven different radio tracers can be selected. For some tracers, the injection protocol can either be bolus or infusion. By fitting a compartmental model to various tissues, one should select the model configuration first. The option: 2 parameters, represents single-tissue compartment model; 3 parameters two-tissue irreversible model; and 4 parameters two-tissue reversible model. The input curve is shown in the lower left panel, and TAC curve is given in the lower right panel. Below the residual plot, Chi-Squared is given, which is the sum of the variance-weighted squared differences between data and fit. $\chi_\nu^2 = \chi^2 / \nu$, where ν is the degrees of freedom of the fit. By minimizing the residuals and Chi-Squared value, one can get a model that better fits the measured TACs.

Select one tracer and one tissue curve and guess the model order. Try to adjust the parameters (K_1, k_2, k_3 and k_4)

- How does the curve change when K1 is increased and why?
- How does the curve change when k2 is increased and why?
- How does the curve change when k3 is different from zero (K1, k2 and k4 is unchanged) and why?
- How does the curve change when k4 is different from zero and why?

Try to vary noise in the dataset

- How does the noise influence the fitting, the residuals and Chi-squared values?

Try the exercise with other tracers

- Try to find optimal model for different tracers

Enable the advanced options and select different blood volume (BV) fractions:

- What happens if blood volume fraction is increased?

Finally try with different injection schemes:

- What happens if you continuously inject a constant dose?
- Why could it be a good idea to do a bolus-injection scheme?

PC Exercise 4: Linearization and Reference tissue modelling

idlcourse: Exercise 4: Linear Methods

Purpose

This exercise should give you an idea on how different linearizations can be used when quantifying PET studies.

Patlak(-Gjedde) plot (irreversible models)

Remember the linearization in Patlak-Gjedde (from page 47-48 in the Pharmacokinetic book):

The solution to a two-tissue compartment model is: $C_t = \frac{K_1}{k_2+k_3}\left(k_2 e^{-(k_2+k_3)t} + k_3\right) \otimes C_a$. From this analytic solution a two tissue compartment model can be written with the following rate constants:

$$\kappa_1 = \frac{K_1 k_2}{k_2+k_3}, \quad \kappa_2 = k_2 + k_3 \quad and \quad \kappa_3 = \frac{K_1 k_3}{k_2+k_3}$$

This can be written as two differential equations:

$$\frac{du_1}{dt} = \kappa_1 C_a - \kappa_2 u_1$$

$$\frac{du_2}{dt} = \kappa_3 C_a$$

Linearization of this leads to the following equations:

$$u_1 = \kappa_1 \int_0^t C_a \, d\tau - \kappa_2 \int_0^t u_1 \, d\tau$$

$$u_2 = \kappa_3 \int_0^t C_a \, d\tau$$

The measured signal from the brain scanner is: $C_t = u_1 + u_2$.

From the late time points (stable) where $\frac{du_1}{dt}$ can be assumed to be close to zero, we get the following approximation:

$u_1 = \frac{\kappa_1}{\kappa_2} C_a$, and therefore by substituting u_1 and u_2 :

$$C_t = \frac{\kappa_1}{\kappa_2} C_a + \kappa_3 \int_0^t C_a \, d\tau \,,$$

Further by dividing C_t by C_a gives:

$$\frac{C_t}{C_a} = \frac{\kappa_1}{\kappa_2} + \kappa_3 \frac{\int_0^t C_a \, d\tau}{C_a}$$

From the fitted line we therefore have:

- The metabolic rate $K_i = \frac{K_1 k_3}{k_2+k_3}$ is therefore the same as κ_3 (the slope)
- The distribution volume $V_d = \frac{K_1 k_2}{(k_2+k_3)^2}$ is therefore the same as κ_1/κ_2 (the intercept)

Logan plot (reversible models)

Remember the linearization in Logan (from page 49-50 in the Pharmacokinetic book):

For a decoupled two-tissue compartment model: $\frac{dC_t}{dt} = V_t \kappa_2 C_a - \kappa_2 C_t$ and the distribution volume is $V_t = \frac{K_1}{\kappa_2}$ and $\kappa_2 = \frac{k_2 k_4}{k_2 + k_3 + k_4}$.

Linearization in the Logan approximation: $\frac{\int_0^t C_t \, d\tau}{C_t} = -\frac{1}{\kappa_2} + V_t \frac{\int_0^t C_a \, d\tau}{C_t}$

The slope of the fitted line therefore describes the distribution volume.

Questions

Repeat the exercises with different setups:

After having selected the linear methods the user interface is open. There you can select radio tracers and the injection paradigms at the left. It is also possible to change the amount of noise in the data. Further it is possible to select which region you want to model.

You can play with it but try at least the following setup:

- FDG dataset – cortex region/white matter
- Raclopride – different regions
    - How does it fit, which approximation works best, why?
    - How does it depend on the time points selected for fitting?
    - What about noise in the dataset?
    - Use “Reveal true Parameters” to compare to the “grand truth”
- NMPD - different regions
    - How does it fit, which approximation works best, why?
    - How does it depend on the time points selected for fitting?
    - What about noise in the dataset?
    - Is it a reversible or irreversible tracer?
- Patient comparison
    - Try to include a patient comparison
    - Vary the k3 deficit
    - Vary the noise
    - Vary the length of the available time series
    - Which variable to look into when identifying a deficit: Effect Size or Ratio of Means?
    - Does it vary between substances?
    - With noise do a “Run 250 fits”
    - Is it possible to identify a difference between NC and patients?

idlcourse: Exercise 5: Reference Tissue Models

This exercise will give you an idea on how to investigate the use of reference tissue model (RTM) approaches for estimating receptor binding potential (BP_{ND}) and how to examine the assumptions inherent to these methods. RTM presented here is designed for **reversible** PET radiotracers. The advantage of using RTM is that it avoids the need for arterial blood sampling.

You can play with it but try at least the following setup:

- FMZ dataset – reference region pons and target region cortex
- Raclopride dataset – reference region cerebellum and target region basal ganglia
- DASB dataset – reference region cerebellum and target region dorsal midbrain (try other regions too)
- PIB dataset – reference region cerebellum and target region cortex
    - How does it fit, which approximation works best, why?
    - How does it depend on the time points selected for fitting?
    - What about noise in the dataset (try to press calculate several times with noise in the dataset)?
    - Which injection protocol is optimal?
    - Use “Reveal true Parameters” to compare to the “grand truth”

    - What happens if you select another reference region?
    - What about fixing the k2R value?
    - Is it problematic to estimate $R = \frac{K_1}{K_1^{'}}$?
    - Try to vary t* (start time for fitting), are the parameters then better estimated?
    - Make a comparison to a patient with different degrees of deficit
    - Use the “Run 50 fits” to do a patient group comparison with different amount of noise in the data

PC Exercise 5: Parameter estimation

idlcourse: Exercise 3: Parameter Estimation

Purpose

This exercise is similar to exercise2 ‘Models and rate constants’. However it further explores the elementary principles of parameter estimation of the micro-parameters: compartmental model rate constants, and the macro-parameters: e.g. volumes of distribution. Instead of manually searching for the proper rate constants, a non-linear least-squares optimization is used starting with the initial values of your choice. The initial parameter values have to be chosen carefully, since there is a risk that the parameters will be caught in a local minimum.

Questions

- Select H_2O as the Radiotracer
    - Study the fit, residuals and the estimated parameter values
    - Try different noise level, how does the noise influence the goodness-of-fit, etc.
    - Which model fits the best?
- Select FMZ and Cortex. Select noise level Low or Med or High. Then you can enable Run Multiple Fits.
    - Try both single-tissue compartment model and two-tissue reversible compartment model. Which one fits best?
    - Run multiple fits 25 times (default). Study the plot of K_1 vs. *Vt*. Look at the bias and variance (Mean and SD) in the micro-parameter estimation (K_i). Look at the bias and variance in the macro-parameter estimation too (V_{nd}, V_s, V_t, and BP_{nd}). Also pay attention to the goodness-of-fit and the precision (COV) of the parameter estimates. Try to vary the model order and look at the *Vt* estimate.
- Select other tracers or regions and keep playing. Which parameters, in general, can be estimated with greater precision, micro-parameters or macro-parameters?